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The Patent Office
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1. Your reference — LLK/PMS/PB60432P

2. Patent application number
(The Patent Office will fill in his part) — 11 AUG 2003 — 0318824.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if you know it)*
08916660001

If the applicant is a corporate body, give the country/state of its incorporation
PUERTO RICO

4. Title of the invention — Novel Composition

5. Name of your agent *(if you have one)*

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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11. We request the grant of a patent on the basis of this application

Signature M Gibson Date 11-Aug-03

12. Name and daytime telephone number of person to contact in the United Kingdom: M Gibson 01279 644841

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PB60432P

Novel Composition

The present invention relates to an oral dosage form comprising 5-[4-[2-(N-methyl-N-(2 pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound A') or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent, to a process for preparing such a dosage form and to the use of such a dosage form in medicine.

The use of a coating to control the rate of release of an active agent has received considerable attention and many different devices have been developed for such a purpose. For example, International Patent Application, Publication Number WO 01/05430 describes a drug delivery device that enables the delivery of drug substances which exhibit pH dependent solubility, in particular compounds that are more soluble at low pH levels (less than pH 2) than at near neutral levels (greater than about pH 5). Such delivery devices are characterised by the presence of a coating that is impermeable and insoluble in the fluid of the environment of use.

International patent application, Publication Number WO 95/30422 describes a series of controlled-release dosage forms of azithromycin. In particular, there is described a series of dosage forms that reduce the exposure of the upper GI tract (e.g. the stomach) to high concentrations of azithromycin, by the use of a pH dependent coating. Such dosage forms do not feature openings through which release of the drug substance may occur.

US Patent Number 6,099,859 describes a controlled release tablet for the delivery of an antihyperglycaemic drug, which comprises an osmotically active drug-containing core and a semipermeable membrane, wherein the semipermeable membrane is permeable to the passage of water and biological fluids and is impermeable to the passage of the drug substance. The semipermeable membrane contains at least one passageway for the release of the antihyperglycaemic drug.

Additional devices that utilise a coating to control the rate of release of an active agent are discussed in US Patent Number 5,004,614. This patent describes a tablet core provided with an outer coating that is substantially impermeable to environmental fluid. The said outer coating may be prepared

from materials that are either insoluble or soluble in the environmental fluids. Where a soluble material is used, the coating is of sufficient thickness that the core is not exposed to environmental fluid before the desired duration of the controlled release of the active agent has passed. Through this impermeable outer coating, one or more opening(s) has been created, so as to provide environmental fluids with an access route to the core. Therefore, upon ingestion of the coated tablet, gastro-intestinal fluid can enter the opening(s) and contact or penetrate the core, to release the active agent. The result is that the active agent is released in a controlled manner out of the opening(s) only. The preferred geometry is such that there is a circular hole on the top and bottom face of the coated tablet. The opening(s) in question have an area from about 10 to 60 percent of the face area of the coated tablet. The rate of drug release is found to be directly related to the diameter of the opening(s) and to the solubility of the matrix core and active agent, allowing the possibility for a variety of drug release profiles be it zero or first order release.

The substantially impermeable coatings of US 5,004,614 are not suitable for the controlled release of all active agents, especially pharmaceutically active weak bases or pharmaceutically acceptable salts and solvates thereof. Such active agents exhibit a marked pH dependent solubility, *i.e.* they are more soluble at around pH 2, associated with regions found in the stomach, compared to their solubility in the generally neutral conditions of the small intestine, around pH 7.

International Patent Application Number PCT/GB03/00594 discloses an oral dosage form comprising an erodable core which contains a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof, such as Compound A, the core having a coating with one or more openings leading to the core, and the coating being erodable under predetermined pH conditions. This provides a beneficial means for administration of a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof, such as Compound A, where it is desirable that release of the active compound takes place in more than one pH environment, based on the finding that it is also beneficial for the coating to be erodable or soluble in a pH dependent manner.

We have now found that the oral dosage form described in International Patent Application Number PCT/GB03/00594 may be beneficially used as a platform for the delivery of more than one active agent, such as, for example, Compound A or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent. To this end the said oral dosage form provides a beneficial means for delivering the other antidiabetic agent, where the antidiabetic agent has a narrow absorption window.

European Patent Application, Publication Number 0 306 228 A1 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0 306 228 A1 is Compound A. International Patent Application, Publication Number WO 94/05659 discloses certain salts of Compound A including the maleate salt at Example 1 thereof. Compound A or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0 306 228 and WO 94/05659. The disclosures of EP 0 306 228 and WO 94/05659 are incorporated herein by reference.

Compound A and pharmaceutically acceptable salts or solvates thereof have useful pharmaceutical properties. In particular, Compound A or a salt or solvate thereof is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof; Alzheimer's Disease and psoriasis.

International Patent Application, Publication Number WO 00/28989 describes various modified release pharmaceutical compositions comprising Compound A or a pharmaceutically acceptable salt or solvate thereof, and another antidiabetic agent.

Suitable other antidiabetic agents according to the present invention include alpha glucosidase inhibitors, biguanides and insulin secretagogues.

A suitable alpha glucosidase inhibitor is acarbose. Other suitable alpha glucosidase inhibitors are emiglitate and miglitol. A further suitable alpha glucosidase inhibitor is voglibose.

Suitable biguanides include metformin, buformin or phenformin, especially metformin. A preferred pharmaceutically acceptable salt of metformin is the hydrochloride salt.

Suitable insulin secretagogues include sulphonylureas.

Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, glimepiride, tolazamide and tolbutamide. Further sulphonylureas include acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide. Also included is the sulphonylurea glipentide.

Further suitable insulin secretagogues include repaglinide. An additional insulin secretagogue is nateglinide.

Compound A and pharmaceutically acceptable salts or solvates thereof, in particular the maleate salt, are known to exhibit marked pH dependent solubility, *i.e.* they are more soluble in the acidic conditions of the stomach (around pH 2) than in the near neutral conditions of the lower intestine (around pH 7).

Certain antidiabetic agents, such as metformin, are known to have a narrow absorption window. It is therefore preferable that such agents are delivered substantially exclusively in a particular pharmacological environment, such as the stomach.

Thus, it is an object of the present invention to provide an oral dosage which compensates for the pH dependent solubility of Compound A or a pharmaceutically acceptable salt or solvate thereof, and which compensates for the narrow absorption window of certain other antidiabetic agents, such as metformin, by providing delivery of the other antidiabetic agent substantially exclusively in a particular pharmacological environment, such as the stomach. Such a dosage form is indicated to provide a maximum beneficial effect on glycemic control for an extended period of time. Such a dosage form is also considered to be suitable for once daily administration.

Accordingly, in its broadest aspect the present invention provides an oral dosage form comprising an erodable core which comprises Compound A or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent, the core having a coating with one or more openings leading to the core, characterised in that the coating is erodable under predetermined pH conditions.

The present invention further provides an oral dosage form comprising, (i) an erodable core, which core comprises Compound A or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent; and

(ii) an erodable coating around said core, which coating comprises one or more openings extending substantially completely through said coating but not substantially penetrating said core and communicating from the environment of use to said core;

characterised in that release of Compound A or a pharmaceutically acceptable salt or solvate thereof and the other antidiabetic agent from the erodable core occurs substantially through the said opening(s) and through erosion of said erodable coating under pre-determined pH conditions.

The above reference to the coating being erodable includes the situation where the coating disintegrates partially or wholly, or dissolves, or becomes porous, on contact with an environmental fluid so as to allow the fluid to contact the core. Suitably, the coating disintegrates partially. Suitably, the coating disintegrates wholly. Suitably, the coating dissolves. Suitably, the coating becomes porous.

Similarly the references to the core being erodable includes the situation where the core disintegrates partially or wholly, or dissolves, or becomes porous, on contact with an environmental fluid so as to allow the fluid to contact the active agent. Suitably, the core disintegrates partially. Suitably, the core disintegrates wholly. Suitably, the core dissolves. Suitably, the core becomes porous.

While this invention provides that erosion of the coating is pH-dependent, the core may release Compound A or a pharmaceutically acceptable salt or solvate thereof and the other antidiabetic agent by eroding in a non-pH dependent manner. However, to suit a specific demand, the core may be a material which allows pH dependent erosion or disintegration of the core to release Compound A or a pharmaceutically acceptable salt or solvate thereof and the other antidiabetic agent from its matrix.

Suitably, the core is arranged to provide immediate release of Compound A or a pharmaceutically acceptable salt or solvate thereof and the other antidiabetic agent. Most suitably, the core is formulated so as to be erodable to substantially the same extent under both the stomach and the intestines.

So that the opening(s) in the coating retains its integrity and control of release rate, it is desirable that the pH dependent erosion of the coating has a defined threshold, i.e. the coating does not substantially erode except in the

intestines. Thus, it is envisaged that erosion of the coating has a defined, pre-determined pH threshold at which it dissolves. Preferably, the coating erodes at pH > 4.5. More preferably, the coating erodes in the pH range from 4.5 to 8. Most preferably, the coating erodes in the pH range 5 to 7.

The use of a coating that erodes rapidly on exiting the stomach environment has been found to be particularly beneficial where the other antidiabetic agent, such as metformin, has a narrow absorption window. In such circumstances any active agent that is not released in the stomach is rapidly delivered on entry into the small intestine, thereby minimising any loss in absorption associated with delivery lower down the GI tract.

The present invention finds particular use in the situation where the coating erodes in the pH conditions of the intestines. Accordingly, the present invention also provides an oral dosage form comprising an erodable core which contains Compound A or a pharmaceutically acceptable salt thereof and another antidiabetic agent, the core having a coating with one or more openings leading to the core, characterised in that the coating is erodable under the pH conditions prevailing in a mammalian intestine.

It will be appreciated that the use of a coating that erodes at pH > 4.5 will restrict the amount of drug released into the acidic conditions associated with the stomach, since release is at low pH levels is substantially limited to diffusion of the active agent through the opening(s) in the erodable coating. Thus, the present invention is indicated to address the problem of "dose dumping" in the stomach for compounds that are more soluble in the pH range from 1 to 3 than in the pH range from 4.5 to 8. As the dosage form leaves a low pH environment and then encounters a higher environmental pH, e.g. moves from the stomach into the intestine, the coating will start to dissolve and erode away to expose all of the tablet core. During coat erosion, the available surface area to release drug is increased. The decrease in drug solubility and therefore rate of drug absorption in the intestine can be compensated for by the increase in the surface area due to all the faces of the tablet core being exposed to erosion. The result is a more balanced drug release profile in both environments.

Where the oral dosage form comprises an antidiabetic agent which is known to have a narrow absorption window, such as metformin, the dosage form is preferably formulated to provide delivery of the antidiabetic agent substantially

exclusively in a particular pharmacological environment, such as the stomach. Where substantially exclusive delivery of the other antidiabetic agent in the stomach is required, the oral dosage form is suitably formulated to reside in the gastric environment over an extended period of time. Increased gastric retention times may be achieved, for example, by increasing the size of the dosage form, and/or administering the dosage form with food.

In applying the concepts of this invention, Compound A or a pharmaceutically acceptable salt or solvate thereof and the other antidiabetic agent may be incorporated into a conventional oral tablet or controlled release matrix (including both swellable and non-swellable systems). The matrix is formed into cores which are then coated with a material with pH-dependent erodability, for example a coating soluble at pH > 4.5, such as a polymethacrylate copolymer. One or more openings may then be drilled through the coatings using conventional techniques as disclosed in US 5,004,614.

According to a further aspect of the present invention, there is provided a process for the preparation of an oral dosage form according to the present invention, which process comprises:

(a) preparing an erodable tablet core;

(b) coating the core with a material with pH-dependent erodability; and

(c) creating one or more openings in the coating, said opening(s) extending substantially completely through said coating but not substantially penetrating said core and communicating from the environment of use to said core.

The core may be prepared by compressing suitable ingredients to form a compacted mass, which comprises the core of the dosage form (also referred to herein as "tablet core"). This may be prepared using conventional tablet excipients and formulation compression methods. Thus, the core typically comprises the active agents along with excipients that impart satisfactory processing and compression characteristics such as diluents, binders and lubricants. Additional excipents that may form part of the core of the device include disintegrants, flavourants, colorants, release modifying agents and/or solubilising agents such as surfactants, pH modifiers and complexation vehicles.

Suitable materials for the core include erodable polymethylmethacrylate resins such as the Eudragit™ series, for example Eudragit™ L30D, saccharoses,

for example lactose and maltose, and cellulose esters, for example methylcellulose, hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose, magnesium stearate, sodium starch glycolate and povidone (polyvinylpyrrolidone). Suitably, the core is predominantly microcrystalline cellulose, hydroxypropylmethylcellulose, lactose and povidone. More suitably, the core consists essentially of hydroxypropylmethylcellulose, lactose, microcrystalline cellulose, sodium starch glycolate, povidone and magnesium stearate.

Typically the active agents and excipients are thoroughly mixed prior to compression into a solid core. The core of the device may be formed by wet granulation methods, dry granulation methods or by direct compression. The core may be produced according to any desired pre-selected shape such as bi-convex, hemi-spherical, near hemi-spherical, round, oval, generally ellipsoidal, oblong, generally cylindrical or polyhedral, e.g. a triangular prism shape. The term "near hemi-spherical" is intended to be construed in the manner described in US 5,004,614. Suitably the core is formulated into a bi-convex shape, e.g. having two domed opposite surfaces. In addition, the core may be produced in a multi-layered (e.g. bi- or tri- layered) form.

A suitable dosage for of Compound A or a pharmaceutically salt or solvate thereof when used in accordance with the present invention is up to 12 mg, for example, 1 to 12 mg. Thus, suitable dosage forms comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 2 to 4 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 4 to 8 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 8 to 12 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

One dosage form comprises 2 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Preferred dosage forms comprise 4 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Preferred dosage forms comprise 8 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Suitable dosages, preferably unit dosages, of the other antidiabetic agent, such as the alpha glucosidase inhibitor, a biguanide or insulin secretagogue, include the known permissible doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications.

For the alpha glucosidase inhibitor, a suitable amount of acarbose is in the range of from 25 to 600 mg, including 50 to 600 mg, for example 100 mg or 200 mg.

For the biguanide, a suitable dosage of metformin is between 100 to 3000 mg, for example 250, 500 mg, 850 mg or 1000 mg, especially 500 mg and 1000 mg.

For the insulin secretagogue, a suitable amount of glibenclamide is in the range of from 2.5 to 20 mg, for example 10 mg or 20 mg; a suitable amount of glipizide is in the range of from 2.5 to 40 mg; a suitable amount of gliclazide is in the range of from 40 to 320 mg; a suitable amount of tolazamide is in the range of from 100 to 1000 mg; a suitable amount of tolbutamide is in the range of from 1000 to 3000 mg; a suitable amount of chlorpropamide is in the range of from 100 to 500 mg; and a suitable amount of gliquidone is in the range of from 15 to 180 mg. Also a suitable amount of glimepiride is 1 to 6 mg and a suitable amount of glipentide is 2.5 to 20 mg.

A suitable amount of repaglinide is in the range of from 0.5 mg to 20 mg, for example 16 mg. Also a suitable amount of nateglinide is 90 to 360 mg, for example 270 mg.

The core may be coated with a suitable pH dependent erodable material by any pharmaceutically acceptable coating method. Examples include coating methods disclosed in US 5,004,614 and film coating, sugar coating, spray coating, dip coating, compression coating, electrostatic coating. Typical methods include spraying the coating onto the tablet core in a rotating pan coater or in a fluidised bed coater until the desired coating thickness is achieved.

Suitably the coating is provided to add about 4 to 8 mg/ cm^2 or 5 - 7 mg/ cm^2 of dry polymer around the tablet surface area. Typically this results in an increase in weight (relative to the core) of from 3 – 10% or 5 – 10 % by weight. Suitably, the coating has a thickness in the range 0.05 to 0.5 mm.

Materials and their blends suitable for use as a pH-dependent erodable coating material in this invention include various polymethacrylate polymers, co-processed polyvinylacetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, shellac, hydroxyropylmethylcellulose phthalate polymers and their copolymers.

The coating material is suitably selected so that it is insoluble in stomach acid i.e. at pH 1.5 – 2, and is soluble or erodable in the small intestine i.e. at around pH 5.5 or in the large intestine i.e. at around pH 7. To achieve this, typically the material of the coating is erodable at pH of 4.5 or above.

Suitably, the coating material is selected from:

cellulose acetate trimellitate (CAT) dissolving @ pH 4.8,
polyvinyl acetate phthalate dissolving @ pH 5.0,
hydroxypropylmethylcellulose phthalate 50 dissolving @ pH 5.2,
hydroxpropylnethylcellulose phthalate 55 dissolving @ pH 5.4,
Acryl-eze™ dissolving @ pH 5.5,
Aquateric™ dissolving @ pH 5.8,
cellulose acetate phthalate dissolving @ pH 6.0,
Eudragit™ L30 D dissolving @ pH 5.5,
Eudragit™ L dissolving @ pH 6.0,
Eudragit™ S dissolving @ pH 6.8, and
shellac dissolving @ pH 7.2.

When necessary, the erodable coating may be modified by addition of plasticisers or anti-tack agents. Suitable materials for this purpose include waxy materials such as glycerides, for example glyceryl monostearate.

Typical sizes for the opening(s), when circular, to be formed in the coating are in the range 0.5 mm – 8 mm of diameter, such as 1, 2, 3 or 4 mms in diameter, depending on the overall size of the tablet and the desired rate of release. The opening(s) may have any convenient geometrical shape, but a rounded shape, e.g. substantially circular or elliptical, is generally preferred.

More elaborate shapes, such as text characters or graphics, may also be formed, provided that the release rate can be made uniform in individual dosage forms. Typical sizes of non-circular openings are equivalent in area to the above mentioned sizes for circular openings, thus in the range of from about 0.19 to about 50.3 mm^2.

For the purposes of the present invention, the term "opening" is synonymous with hole, aperture, orifice, passageway, outlet etc.

The opening(s) may be formed by methods disclosed in US 5,004,614. Typically opening(s) may be formed by drilling, for example using mechanical drill bits or laser beams, or by punches that remove the cut area. The formation of the opening(s) may by default remove a small portion of the exposed core. It is also possible to purposely form a cavity below the aperture as a release rate controlling device, the cavity exposing a greater initial surface area of core than a flat surface. Suitably, the opening(s) extend through the entire erodable coating such that there is immediate exposure of the core to the environmental fluid when the device is placed in the desired environment of use.

Also it is possible to form the opening(s) *in situ* when the dosage form is administered, by forming a coating containing pore-forming agents i.e. material that will dissolve in the stomach to create pores in the coating. Accordingly, there is also provided an oral dosage form comprising,

(i) an erodable core, which core comprises Compound A or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent; and

(ii) an erodable coating surrounding said core, which coating comprises a pore forming agent that is erodable in the pH range from 1 to 3 to form one or more openings extending substantially completely through said coating but not substantially penetrating said core and communicating from the environment of use to said core;

characterised in that release of Compound A or a pharmaceutically acceptable salt or solvate thereof and the other antidiabetic agent from the dosage form occurs through the said opening(s) by the erosion of said erodable core and through erosion of said erodable coating under pre-determined pH conditions.

In US 5,004,614, the opening(s) preferably comprise about 10 - 60 % of the total face area of the tablet i.e. the upper and lower surfaces of a biconvex

tablet. In the present invention, the opening(s) may comprise 0.25 to 70%, such as 10 – 70% of the total face area.

Alternatively, it may be useful to characterise the rate controlling effect of the opening(s) by reference to the area of the opening(s) relative to the total surface area of the coated tablet. Additionally, especially in cases where the core erodes by undercutting of the edges of the opening(s), the rate controlling effect may be related to the total circumference of the opening(s).

An unexpected finding is that two openings, for example one on each primary surface of a biconvex tablet, release an active agent from the core at a rate marginally greater than that of a single opening of the same overall area. However the variability of the release rate from the two openings is less than the variability of release rate from the corresponding single opening. Therefore, in the preferred embodiment of the invention, the coating of the core is provided with two, or more than two, apertures leading to the core. More preferably, the erodable coating surrounding the core is provided with two, or more than two, openings extending substantially completely through said coating but not substantially penetrating said core and communicating from the environment of use to said core.

Where more than one opening is provided, the openings may be located on the same face of the oral dosage form, or on different faces. Suitably, the oral dosage form has two openings, one on each opposing face. Suitably, the oral dosage form is a tablet having two opposed primary surfaces, each surface having one opening through the coating.

As a protection for the core material, to prevent contamination via the opening(s) before dosing, it may desirable to provide a conventional seal coating to either the core, or to the dosage form after formation of the opening(s). The seal coat may be a sub-coat or over-coat to the erodable coating.

By adjustment of the above variables and the surface area of the exposed core, the release rates in the different environmental conditions can be harmonised to obtain comparable release rates under different body environments, and so achieve more constant dosing to a patient.

Preferably the dissolution rates of the oral dosage forms of this invention are arranged, for example by routine adjustment of the erodable coating and dimensions of the opening(s), so that the rate of release is substantially similar in

the different pH environments experienced by the dosage form on administration. Dissolution rates may be assessed by *in vitro* testing in solutions of the appropriate pHs. For example, when comparing dissolution in the stomach and intestine, tests may be carried out initially at pH 1.5 with a transfer to pH 6.8 after 2 hours or 4 hours, as an assumed time for residence in the stomach before emptying into the intestines of a notional patient in respectively fasted and fed conditions. Alternatively, tests may be carried out initially at pH 4.0, to simulate a fed stomach environment, with a transfer to pH 6.8 after 5 hours.

In a preferred embodiment the present invention provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, which method comprises administering an oral dosage form of this invention comprising Compound A or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent, to a human or non-human mammal in need thereof.

The present invention further provides a method for the treatment and/or prophylaxis of Alzheimer's disease, which method comprises administering an oral dosage form of this invention comprising Compound A or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent, to a human or non-human mammal in need thereof.

In yet a further aspect of the present invention, there is provided a method for the treatment and/or prophylaxis of psoriasis, which method comprises administering an oral dosage form of this invention comprising Compound A or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent, to a human or non-human mammal in need thereof.

In accordance with the present invention, it will be understood that the Compound A and the other antidiabetic agent are in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate to the relevant pharmaceutically active agent chosen. In certain instances herein the names used for the antidiabetic agent may relate to a particular pharmaceutical form of the relevant active agent. It will be understood that all pharmaceutically acceptable forms of the active agents per se are encompassed by this invention.

Suitable pharmaceutically acceptable forms of the insulin sensitiser and other antidiabetic agent depend upon the particular agent used but included are known pharmaceutically acceptable forms of the particular agent chosen. Such derivatives are found or are referred to in standard reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and the above-mentioned publications. For example, a particular form of metformin is metformin hydrochloride, a particular form of repaglinide is a benzoic acid salt form and a particular form of tolbutamide is a sodium salt form.

As used herein the term "pharmaceutically acceptable" embraces compounds, compositions and ingredients for both human and veterinary use. For example the term "pharmaceutically acceptable salt" embraces a veterinarily acceptable salt. In particular, suitable pharmaceutically acceptable salted forms of Compound A include those described in European Patent Number 0 306 228 and International Patent Application, Publication Number WO 94/05659. A particularly preferred salt of Compound A is the maleate salt. A preferred pharmaceutically acceptable solvated form of Compound A is a hydrate.

No adverse toxicological effects are indicated in the above mentioned treatments.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

In the following Examples, tablet cores were formed by conventional means by mixing together the active ingredients with excipients and compressing to form the tablet core. These Examples are intended to be by way of illustration rather than limitation of the present invention and the combination of Compound A and metformin is used simply as one example of a combination suitable for use with the present invention.

Example 1

A core was formed from the following formulation:

	%w/w
Immediate Release Layer	
Compound A (as maleate salt)	0.5
Compound B (as hydrochloride salt)	85.2
Lactose Monohydrate	1.9
Microcrystalline cellulose	5.6
Magnesium stearate	0.5
Hypromellose (HPMC)	3.6
Sodium starch glycolate	0.2
Povidone	2.6

by compression to form a 19.0mm x 9.2mm, oval tablet of 1174 mg.

The tablet cores were coated with a HPMC-based sub-coat and a polymethacrylate resin soluble at pH 5.5 to a total weight of 1246.5 mg.

An opening of diameter 3.0 mm was drilled through the coating in each of the two primary surfaces of the coated cores to expose the surface of the core.

Example 2

A core was formed from the following formulation:

	%w/w
Immediate Release Layer	
Compound A (as maleate salt)	0.5
Compound B (as hydrochloride salt)	85.2
Lactose Monohydrate	1.9
Microcrystalline cellulose	5.6
Magnesium stearate	0.5
Hypromellose (HPMC)	3.6
Sodium starch glycolate	0.2
Povidone	2.6

by compression to form a 19.0mm x 9.2mm, oval tablet of 1174 mg.

The tablet cores were coated with a HPMC-based sub-coat and a polymethacrylate resin soluble at pH 5.5 to a total weight of 1246.5 mg.

An opening of diameter 4.0 mm was drilled through the coating in each of the two primary surfaces of the coated cores to expose the surface of the core.

Dissolution profiles for the dosage forms of Examples 1 and 2, for Compound A and metformin ('Compound B') are shown in Figures 1 and 2 respectively in the accompanying drawings. Dissolution tests were performed initially at pH 4.0, with a transfer to pH 6.8 after 5 hours.

Claims

1. An oral dosage form comprising an erodable core which comprises 5-[4-[2-(N-methyl-N-(2 pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent, the core having a coating with one or more openings leading to the core, characterised in that the coating is erodable under predetermined pH conditions.

2. An oral dosage form according to claim 1, comprising,
(i) an erodable core, which core comprises Compound A or a pharmaceutically acceptable salt or solvate thereof and another antidiabetic agent; and
(ii) an erodable coating around said core, which coating comprises one or more openings extending substantially completely through said coating but not substantially penetrating said core and communicating from the environment of use to said core;
characterised in that release of Compound A or a pharmaceutically acceptable salt or solvate thereof and the other antidiabetic agent from the erodable core occurs substantially through the said opening(s) and through erosion of said erodable coating under pre-determined pH conditions.

3. An oral dosage form according to claim 1, comprising an erodable core which contains Compound A or a pharmaceutically acceptable salt thereof and another antidiabetic agent, the core having a coating with one or more openings leading to the core, characterised in that the coating is erodable under the pH conditions prevailing in a mammalian intestine.

4. A process for the preparation of an oral dosage form according to claim 1, which process comprises:
(a) preparing an erodable tablet core;
(b) coating the core with a material with pH-dependent erodability; and

(c) creating one or more openings in the coating, said opening(s) extending substantially completely through said coating but not substantially penetrating said core and communicating from the environment of use to said core.

5. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, which method comprises administering an oral dosage form according to claim 1, to a human or non-human mammal in need thereof.

6. A method for the treatment and/or prophylaxis of Alzheimer's disease, which method comprises administering an oral dosage form according to claim 1, to a human or non-human mammal in need thereof.

7. A method for the treatment and/or prophylaxis of psoriasis, which method comprises administering an oral dosage form according to claim 1, to a human or non-human mammal in need thereof.

Figure 1

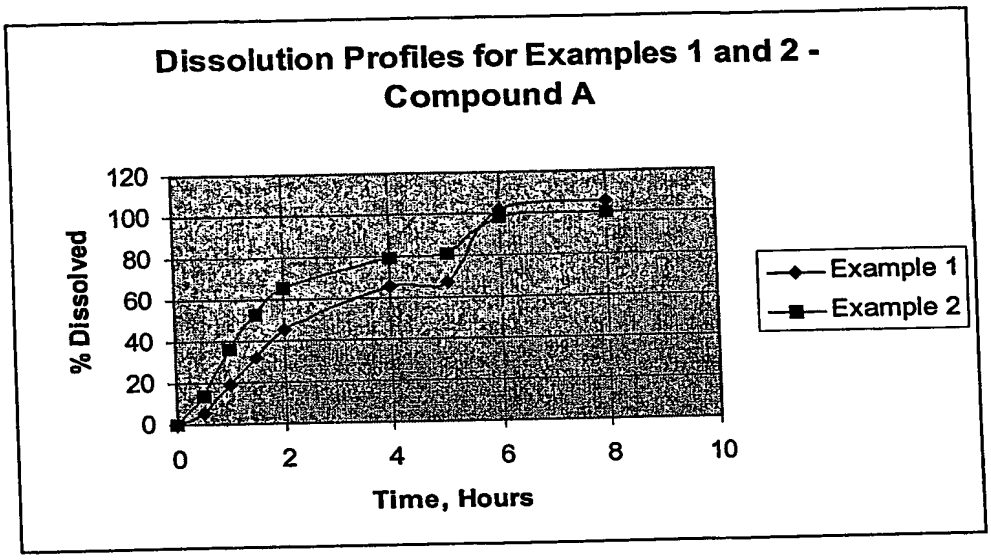
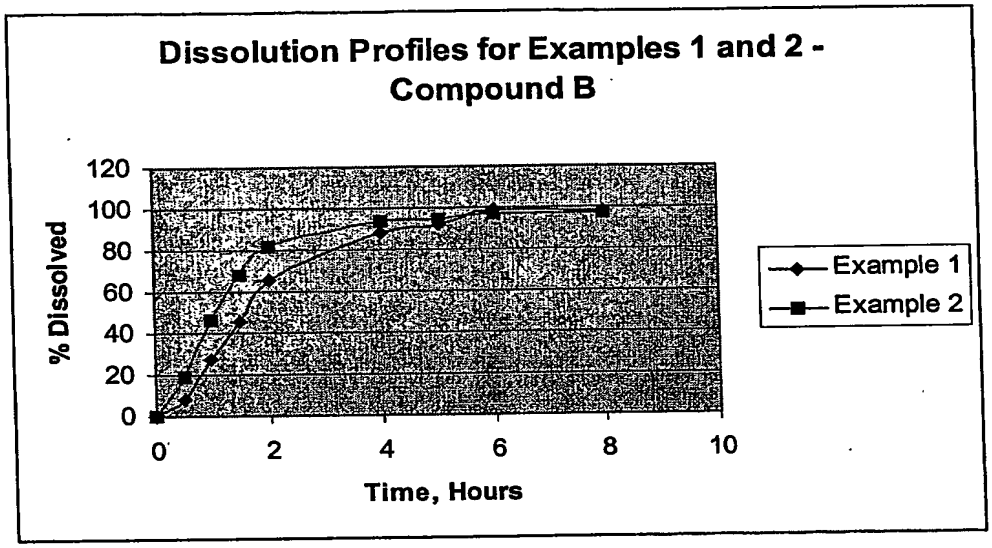

Dissolution Profiles for Examples 1 and 2 - Compound A
% Dissolved
120
100
80
60
40
20
0
0
2
4
6
8
10
Time, Hours
Example 1
Example 2

Figure 2


Dissolution Profiles for Examples 1 and 2 - Compound B
% Dissolved
120
100
80
60
40
20
0
0
2
4
6
8
10
Time, Hours
Example 1
Example 2

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